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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/985,936	KAPPELER ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-16,35-40 and 49-51* is/are pending in the application.

4a) Of the above claim(s) *35-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-16 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10,11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 2-16, 35-40, 49-51 are pending.

Applicant's cancellation of claims 1, 17-34, 41-48 and amendment of claims 2, 4-5, 7-8, 10, 13-14, 35, 37-38 in Paper No. 4, filed on 2/20/2002 is acknowledged.

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 2-16, 49-51, drawn to a DNA construct comprising a nucleic acid which encodes a non-bovine pre-prochymosin, prochymosin or chymosin or a fusion protein comprising a pre-prochymosin, prochymosin, or chymosin, host cells and expression of such DNA construct, classified in class 435, subclass 69.1.

   II. Claims 35-40, drawn to a composition comprising a non-bovine pre-prochymosin, prochymosin, or chymosin, and a method of manufacturing cheese with said non-bovine proteins, classified in class 435, subclass 23.

The inventions are distinct, each from the other because of the following reasons:

2. Groups I and II each comprise a chemically unrelated structure capable of separate manufacture, use, and effect. The DNA in Group I comprises nucleotides whereas the protein of Group II comprises amino acids. The DNA has other uses besides encoding the protein of Group II such as a hybridization probe or in gene therapy. The protein of Group II can be prepared by processes which are materially different from recombinant DNA expression of Group I, such as by chemical synthesis, or by isolation and purification from natural sources.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Mr. Iver Cooper on 3/13/2003 a provisional election was made with traverse to prosecute the invention of Group I, claims 2-16 and 49-51. Affirmation of this election must be made by applicant in replying to this Office action.

5. Claims 35-40 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

7. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 09/705,917, filed on 11/06/2000.

Information Disclosure Statement

8. The information disclosure statements (IDS) submitted on 5/23/2002 and 9/23/2002 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Oath/Declaration

9. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because there is no date next to the signature of Inventor Henrik Rahbek-Nielsen.

Drawings

10. The drawings have been reviewed and are objected under 37 CFR 1.84 or 1.152. See attached Notice of Draftsperson's Patent Drawing Review. Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDOMENT of the application. In addition, if amendments to the specification are needed due to drawing corrections, Applicant is requested to submit such amendments while the case is being prosecuted to expedite the processing of the application.

Claim Objections

11. Claim 7 is objected to because of the following informalities: the term "prochymosin or chymosin, or a fusion protein thereof" should be replaced with "prochymosin, chymosin, or a fusion protein thereof". Appropriate correction is required.

12. Claim 13 is objected to because of the recitation of "but with a coding sequence....". Since the conditions under which the production of pre-prochymosin, prochymosin or chymosin are identical and the vector is the same, it is implied that the only difference is the

polynucleotides encoding such proteins. Therefore, for clarity, it is suggested that the term be deleted. Appropriate correction is required.

13. Claim 51 is objected to because of the recitation of "if said expressible protein is a fusion protein, cleaving it to release said protein of interest". For clarity, applicants may wish to delete the cleaving step in claim 51 and instead amend dependent claim 5 to further add the cleaving step. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 2-16 and 49-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

16. Claim 49 (claims 2-16 and 50-51 dependent thereon) is indefinite in the recitation of "protein which is (I) (a) a non-bovine pre-prochymosin....or (b) a fusion protein comprising ..., and cleavable to release said core protein; and (II) appropriate expression signals, operably linked to said coding sequence.." for the following reasons. As written, (I) and (II) appear to refer to characteristics or properties of the protein however it is unclear how "appropriate expression signals" is related to the protein. Furthermore, it is unclear as to how (I) and (a) or (b) are related. In addition, it is unclear if the term "non-bovine" applies to all the proteins recited. For examination purposes, it will be assumed that the claim is drawn to a DNA construct comprising a polynucleotide encoding an expressible protein selected from the group

consisting of (a) a non-bovine pre-prochymosin, (b) any prochymosin, (c) any chymosin, and (d) any cleavable fusion protein comprising any pre-prochymosin, any prochymosin or any chymosin, wherein said polynucleotide is operably linked to expression signals which allow expression of the protein in a host cell. Correction is required.

17. Claim 51 (claims 2-8, 10-11, 13-16 dependent thereon) is indefinite in the recitation of "non-bovine pre-prochymosin, prochymosin, and chymosin" since it is unclear if the term "non-bovine" refers to pre-prochymosin only or if it applies to the other proteins recited. For examination purposes, the term will be interpreted as "non-bovine pre-prochymosin, any prochymosin, and any chymosin". Correction is required.

18. Claim 2 (claim 3 dependent thereon) is indefinite in the recitation of "wherein the coding sequence is derived from a mammalian species selected from the group consisting of ....., and Equidae species and a primate species" for the following reasons. As known in the art, a sequence is a graphical representation of the order in which nucleotides/amino acids are arranged in a polynucleotide/polypeptide. Therefore, it is unclear as to how a sequence is derived from an animal. In addition, the term "and Equidae species and a primate species" is unclear since it appears as if the "sequence" is derived from one of the species recited and a primate species. For examination purposes, the claim will be interpreted as being drawn to the method of claim 51 wherein the polynucleotide is isolated from a mammalian species selected from the group consisting of a ruminant species, a Camelidae species, a porcine species, an Equidae species and a primate species. Correction is required.

19. Claim 4 is indefinite in the recitation of "coding sequence for pre-prochymosin .....is isolated or derived from Camelus dromedaries" for the following reasons. As indicated above, a

sequence is a graphical representation therefore it is unclear how a sequence can be derived from an animal. In addition, the recitation of "isolated or derived" is confusing since it implies that "isolated" is not equivalent to "derived" and there is no definition of the meaning of the term "derived". For examination purposes, the claim will be interpreted as being drawn to a method according to claim 51 wherein the polynucleotide encoding pre-prochymosin, prochymosin or chymosin is isolated from Camelus dromedaries.

20. Claim 8 is indefinite in the recitation of "the expression vector" since there is no antecedent basis for the vector. For examination purposes, it will be assumed that the term "expression vector" is equivalent to "DNA construct". Correction is required.

21. Claim 8 is indefinite in the recitation of "pGAMpR as described in Ward et al., 1990" as it is unclear which vector is being referred to. The recitation of "Ward et al., 1990" is an improper incorporation of essential material (i.e. structure of the vector) by reference. Correction is required.

22. Claim 8 is indefinite in the recitation of "substituting the coding sequence ...with a coding sequence for ..." for the following reasons. As indicated above, a sequence is a graphical representation of how a molecule (polynucleotide or polypeptide) is arranged. Therefore, what is being substituted in the vector is the polynucleotide encoding the proteins recited in the claim. For examination purposes, the term will be interpreted as "substituting the polynucleotide encoding bovine prochymosin in that vector with the polynucleotide encoding the non-bovine pre-prochymosin....". Correction is required.

23. Claim 13 is indefinite in the recitation of "with a coding sequence for bovine...in place of the coding sequence for ..." for the reasons discussed in regard to claim 8. For examination

purposes, the term will be interpreted as "with the polynucleotide encoding the bovine pre-prochymosin

24. Claim 15 (claim 16 dependent thereon) is indefinite in the recitation of "claim 1" since claim1 has been cancelled. For examination purposes, the claim will be interpreted as being dependent upon claim 51. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

25. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

26. Claims 2-8, 10-11, 13-16 and 49-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 49 is drawn to genera of DNA construct comprising any non-bovine pre-prochymosin, any prochymosin (from any source), or any chymosin (from any source). Claim 50 is drawn to genera of host cells comprising said genera of DNA constructs. Claims 2-3, 5-8, 10-11, 13-16 and 51 are drawn to a method of producing the protein encoded by the DNA construct of claim 49. Claim 4 is drawn to a method of producing any camel chymosin, pre-prochymosin, or prochymosin. While the specification has disclosed a method for recombinant production of a single camel chymosin, prochymosin, or pre-prochymosin encoded by the polynucleotides contained in biological deposits CBS 108915 and CBS 108916 , there is no

disclosure of the structure of DNA molecules encoding other chymosins from other organisms or camel as encompassed by the claims. The specification fails to disclose which are the critical structural elements required in a polynucleotide to encode a polypeptide having chymosin activity. Furthermore, while the specification discloses that the camel chymosin produced by the microorganisms deposited as CBS 108915 and CBS 108916, outperforms bovine chymosin in milk clotting activity, there is no disclosure in the specification of other chymosins from other organisms which also outperform bovine chymosin as recited in the claims. There is also no disclosure of how structure correlates with milk clotting activity. While one could argue that the polynucleotides of the instant claims can be isolated by sequence comparison using the structures disclosed in the instant application or the prior art, the state of the art teaches that sequence comparison alone should not be used to determine function and that small changes can drastically change the function of a polynucleotide/polypeptide. Bork (Genome Research, 10:398-400, 2000) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert

an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The specification only discloses a single species of the genera which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genera as encompassed by the claims. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

27. Claims 2-8, 10-11, 13-16 and 49-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the DNA constructs present in the biological deposits CBS 108915 and CBS 108916, a host cell comprising said DNA constructs, and a method of producing the pre-prochymosin, prochymosin, or chymosin of said constructs, does not reasonably provide enablement for (1) a DNA construct comprising a polynucleotide which encodes any non-bovine pre-prochymosin, any prochymosin, or any chymosin, or (2) a method of producing any non-bovine pre-prochymosin, any prochymosin, or any chymosin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims as described above, is not commensurate with the enablement provided in regard to (1) the extremely large number of unknown pre-prochymosins, prochymosins and chymosins encompassed by the claims, and (2) the lack of knowledge as to which are the structural elements required in a chymosin to have enhanced milk clotting capabilities compared to bovine chymosin. As indicated above, the specification is silent in regard to the structure of other DNA molecules encoding other chymosins, including additional camel chymosins. There is no disclosure of the critical structural elements required in a polynucleotide to encode a polypeptide having chymosin activity. Furthermore, there is no disclosure of how structure correlates with milk clotting activity. As discussed above, the state of the art teaches the unpredictability of isolating polynucleotides/polypeptides using structural homology and how small structural changes can result in major changes in function. See the teachings of Bork, Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al. already discussed. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to display chymosin function, the lack of knowledge in regard to the critical structural elements required to display enhanced milk clotting activity, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to screen and isolate those polynucleotides, as encompassed by the claim, with chymosin activity, and further determine if they encode chymosins with enhanced milk clotting activity compared to bovine chymosin. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

28. Claims 9 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel vectors and microorganisms. Since the vectors and microorganisms are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed plasmids sequences are not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the plasmids. The specification does not disclose a repeatable process to obtain the vectors and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of these plasmids should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that applicants have deposited organisms containing said plasmids (page 22, lines 22-25) but there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

a. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

b. all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

c. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

d. the deposit will be replaced if it should ever become non-viable.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

29. Claims 49-51, 5, 7, 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Nomura et al. (Appl. Microbiol. Biotechnol. 42:865-870, 1995). Nomura et al. teaches the production of a fusion protein comprising rat apolipoprotein E (rApoE) and (1) pre, (2) pre-pro, and entire pre-prorennin of Mucor pusillus (MPP, chymosin), in S. cerevisiae (Abstract; page 867, column 1-2). Nomura et al. teaches several vectors (DNA constructs) wherein the rApoE polynucleotide is fused to the DNA encoding the pre, prepro and the entire MPP protein (Figure 2, page 868). The fusion protein produced by Nomura et al. is secreted (Abstract and Title).

Claim 49 is directed to a DNA construct comprising a polynucleotide encoding a non-bovine pre-prochymosin operably linked to expression signals which would allow expression in a host cell. Claim 50 is directed to a host cell comprising said DNA construct. Claim 51 is drawn to a method of producing the pre-prochymosin. Claim 5 is drawn to the method of claim 51 with the added limitation that the prochymosin/chymosin be expressed as a fusion protein. Claim 7 is drawn to the method of claim 51 with the added limitation that the pre-prochymosin is secreted. Claim 10 is directed to the method of claim 51 wherein the host cell is a yeast cell. Therefore, the DNA constructs, S. cerevisiae host cells and the method of production taught by Nomura et al. anticipate the claims as written.

Claim Rejections - 35 USC § 103

30. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

31. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

32. Claims 2, 5-8, 10-11 and 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Houen et al. (Int. J. Biochem. Cell Biol. 28(6):667-675, 1996; cited in the IDS) in view of Ward et al. (Bio/Technology 8:435-440, 1990; cited in the IDS). Houen et al. teaches the amino acid sequence of a porcine prochymosin and porcine chymosin as well as the nucleotide sequence of the corresponding polynucleotides (Figure 2, page 672). Houen et al. does not teach the polynucleotides encoding the porcine prochymosin or the porcine chymosin operably linked to an expression signal. Ward et al. teaches the expression vector pGAMpR (DNA construct) comprising the polynucleotide encoding bovine prochymosin B fused in frame to the A. awamori glucoamylase gene (page 435, second column, lines 18-22; Figures 1 and 2, page 436). The vector was used to transform A. awamori, and secretion of chymosin was obtained (page 435, second column, lines 23-28) after cleavage of chymosin from the glucoamylase-chymosin fusion protein. Ward et al. does not teach a porcine prochymosin or a porcine chymosin.

Claim 49 is directed to a DNA construct comprising a polynucleotide encoding a prochymosin or a chymosin operably linked to expression signals which would allow expression in a host cell. Claim 50 is directed to a host cell comprising said DNA construct. Claim 51 is drawn to a method of producing the prochymosin or chymosin. Claim 2 is drawn to the method of claim 51 with the added limitation that the prochymosin/chymosin polynucleotide be isolated from a porcine species. Claim 5 is drawn to the method of claim 51 with the added limitation that the prochymosin/chymosin be expressed as a fusion protein. Claim 6 is drawn to the method of claim 51 with the added limitation that the fusion protein comprises glucoamylase. Claim 8 is directed to the method of claim 51 wherein the DNA construct used is vector pGAMpR, modified by replacing the DNA encoding the bovine prochymosin with a polynucleotide

encoding another prochymosin. Claims 10-11 are drawn to the method of claim 51 wherein the host cell is a fungal cell or A. awamori.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an expression vector, as taught by Ward et al., with the porcine prochymosin polynucleotide of Houen et al. A person of ordinary skill in the art is motivated to construct such a vector and express the glucoamylase-prochymosin fusion protein because chymosins are commonly used as milk clotting agents in cheese manufacture, therefore improved production of said enzymes is highly desirable. One of ordinary skill in the art has a reasonable expectation of success at making the vector, transforming A. awamori and producing porcine chymosin since Ward et al. teaches the successful production of bovine chymosin using a vector comprising DNA encoding a fusion protein of glucoamylase and bovine chymosin in A. awamori.. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

33. Claims 2-3, 5-8, 10-11 and 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pungercar et al. (Nucleic Acids Research 18(15):4602, 1990) in view of Ward et al. (Bio/Technology 8:435-440, 1990; cited in the IDS). Pungercar et al. teaches the cDNA and primary amino acid structure of lamb preprochymosin and lamb prochymosin (Abstract). Pungercar et al. does not teach a polynucleotide encoding preprochymosin or prochymosin operably linked to expression signals. The teachings of Ward et al. have been discussed above. Ward et al. does not teach the cDNA or the primary amino acid structure of lamb preprochymosin or prochymosin.

The subject matter of claims 2, 5-8, 10-11 and 49-51 has been discussed above. Claim 3 is directed to the method of claim 2 as described above wherein the polynucleotide encoding the preprochymosin/prochymosin is isolated from ovine species.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an expression vector, as taught by Ward et al., with the lamb (ovine) pre-prochymosin/prochymosin polynucleotide of Pungercar et al., transform a host cell and produce the lamb prochymosin. A person of ordinary skill in the art is motivated to construct such a vector and express the glucoamylase-prochymosin fusion protein because chymosins are commonly used as milk clotting agents in cheese manufacture, therefore improved production of said enzymes is highly desirable. One of ordinary skill in the art has a reasonable expectation of success at making the vector, transforming A. awamori and producing ovine chymosin since Ward et al. teaches the successful production of bovine chymosin using a vector comprising DNA encoding a fusion protein of glucoamylase and bovine chymosin in A. awamori.. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

34. No claim is in condition for allowance.

35. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

36. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
April 3, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1600